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Editorial

Title: Hepatic diagnostics in pregnancy: biopsy, biomarkers and beyond.

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Managing liver disease in pregnancy is both complex and challenging. Moreover, accurate diagnosis is critical to decision making, and often the most significant decision is whether to proceed to liver biopsy. Reticence exists among hepatologists and radiologists regarding biopsy procedures in this context. With minimal data to draw from, experience from single-center series and case reports have formed much of the evidence base regarding the safety and efficacy of liver biopsy in pregnancy, albeit such reports being largely limited to patients with autoimmune liver diseases.

The publication of a population-based cohort study assessing the pregnancy outcomes of women who underwent liver biopsy during pregnancy in the current issue of HEPATOLOGY is welcomed, even if some limitations exist in its generalizability.[1] By linking data from the Swedish Medical Birth Registry to the Swedish Patient Registry, Ludvigsson et al identified 23 women over a twenty-year period who had undergone liver biopsy during pregnancy. Seventeen women had a diagnosis of a pre-existing liver condition prior to pregnancy, including two women who had undergone liver transplantation. Notably, 2/6 biopsies performed in women without pre-existing liver disease were for characterization of intrahepatic malignancies. By comparing the pregnancy outcomes of the 23 women who underwent biopsy during pregnancy, to 1.9 million unexposed pregnancies, moderately increased risks of preterm birth and small for gestational age infants were identified.

The study focused on births between 1992 and 2011, with hepatitis C virus reported as the commonest indication for liver biopsy during pregnancy. The widespread availability of transient elastography for the staging of fibrosis and the effectiveness

of direct-acting antiviral therapy in achieving virologic 'cure' has resulted in liver biopsy now being redundant in this context. Furthermore, the majority of women underwent biopsy in the first trimester, with more than 50% of biopsies performed in the first month of pregnancy. It is likely that many women were unaware of their pregnancy at the time of biopsy, making the decision to proceed to biopsy easy for the clinicians concerned. Furthermore, it is plausible that a significant number of biopsies were deferred to the post-partum period, as the number of biopsies undertaken in women with liver disease in the year pre- and post-partum was more than fifteen-fold higher (n=384) than those performed during pregnancy.

Chronic liver disease in itself has been shown to have a negative impact on pregnancy outcomes, with an increased risk of preterm birth reported in women with cirrhosis.[2] In Ludvigsson's study, when the outcomes of women who underwent liver biopsy during pregnancy were compared only to women with pre-existing liver disease, the procedure itself was associated with only an increased risk of a small for gestational age infant. Notably, women who underwent a liver biopsy in the year pre- or post-pregnancy had a greater incidence of adverse pregnancy outcomes, with a substantially increased risk of neonatal death, demonstrating the significant impact liver disease can have on maternal and fetal health.

The issue of how to investigate the pregnant woman with liver enzyme abnormalities or established liver disease (or post liver transplantation) is nuanced, with the absolute need for liver biopsy often a source of anxiety. From this study, we can say that in the first trimester, liver biopsy appears to be relatively safe and well tolerated.

Beyond the first trimester, it is difficult to draw firm conclusions, and each case should be judged on the basis of risk and benefit.

If a woman presents for the first time during pregnancy with liver disease, the work-up is similar to that of the non-pregnant state.[3] A comprehensive history, physical exam, and serological testing should yield a diagnosis for the majority. The pregnancy related physiological changes lead to dilution of hemoglobin and albumin, an elevation in alpha-fetoprotein, and a rise in alkaline phosphatase as a result of production by the placenta. Bilirubin, AST, ALT, GGT, and PT/INR remain largely unchanged and may assist in determining both the etiology and severity of the underlying disease. Ultrasound is safe and remains the imaging modality of choice.

An assessment of liver fibrosis by non-invasive methods may also be useful to assess for chronicity of liver disease, and data is slowly emerging on the safety of transient elastography and acoustic radiation force impulse (ARFI) elastosonography in pregnant women. Further validation will be necessary to accurately characterize the changes in liver elasticity that occur during pregnancy and evaluate the impact of pregnancy related conditions such as pre-eclampsia.[4] Non-invasive scores have been shown in a number of studies to have a reasonable correlation with the histological assessment of liver fibrosis. [5] However, platelet counts decrease during pregnancy, so although the APRI and FIB-4 score may assist in the identification of patients with cirrhosis, their positive predictive value will fall.

First performed in Germany in 1882, and refined by Menghini to the "one-second needle biopsy of the liver" technique in 1958, percutaneous liver biopsy allows

accurate assessment of both liver injury and fibrosis, as well as the enabling the histopathological characterization of tumors.[6] Large cohort studies have demonstrated the safety of the procedure in non-pregnant patients, with a low rate of complications, and a procedural associated mortality of 1/10,000. The major risk is post-biopsy hemorrhage, which is increased in patients with significant thrombocytopenia.[7]

In reality, for women with a suspected pregnancy associated liver disease, liver biopsy should only rarely be necessary, as these conditions tend to have characteristic features in terms of clinical presentation, alterations in laboratory indices and trimester of occurrence. Acute fatty liver of pregnancy has the greatest impact on maternal and fetal health, and although liver biopsy was previously considered essential for confirmation of the characteristic microvesicular steatosis present on histology, biopsy was associated with a significant risk of bleeding in patients with coagulopathy. In recent years, validation of the non-invasive 'Swansea criteria' for diagnosis has largely eliminated the need for biopsy, except in cases where there is clinical uncertainty or an atypical presentation of the disease.[8]

Liver biopsy is most likely to be indicated during pregnancy for selected women with pre-existing liver disease, where the disease is likely to cause significant risk to mother or fetus. A priori, this includes 1) women with a suspicious liver lesion, 2) women with coincident seronegative disease (i.e. suspected autoimmune or other unexplained hepatitis with negative autoantibodies and normal immunoglobulin G levels), or 3) women who have undergone liver transplantation with significant graft dysfunction and unrevealing viral and immune serology. Cardiac output increases

during pregnancy, but hepatic blood flow does not alter significantly, and there were no instances of post biopsy hemorrhage reported in Ludvigsson's study.[9] Potential risks to the fetus from procedural sedation were not explored, but the literature to date would indicate that for a single short procedure, the use of sedation is unlikely to lead to significant neurological sequelae.[10]

To conclude, the data presented in this retrospective cohort study provides support for the safety of liver biopsy in selected women during pregnancy. Important caveats remain. As the majority of women were biopsied in the first trimester of pregnancy, and over half in the first month after conception, the results are not generalizable to women in the later stages of pregnancy. Furthermore, although it is likely that the overwhelming majority of these biopsies were undertaken by the percutaneous route, this has not been confirmed by the authors. For women presenting with liver disease in later pregnancy, the risks and benefits of performing a liver biopsy must be carefully weighed against expectant management, with a view to liver biopsy in the post-partum period.

Figure: Workup of abnormal liver function tests in pregnancy

Figure Legend:

T: Trimester

HELLP: Hemolysis, elevated liver enzymes, and low platelets;

ARFI: acoustic radiation force impulse elastosonography

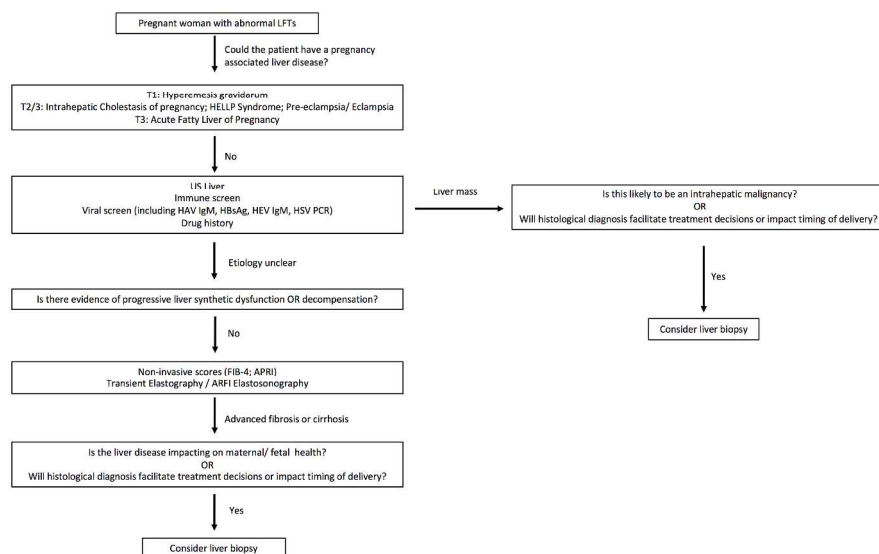
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Workup of abnormal liver function tests in pregnancy

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